REMARKS

Reconsideration of the allowability of the present application in view of the above amendments and the following remarks is requested respectfully.

Status of the Claims

Amendments of an editorial nature have been made to Claims 2 and 21 to 37. Claims 39 to 44 have been added to include recitations that have been excised from Claim 24. Claims now pending are Claims 1, 2, and 21 to 44.

Summary of the Invention

Applicants have developed a novel formulation which comprises an opioid, a CCK-antagonist, and a biphasic carrier. The invention is defined by the following claim forms: (A) a pharmaceutical formulation which comprises an opioid-potentiating amount of a CCK-antagonist, an analgesic amount of an opioid, and a pharmaceutically-acceptable biphasic carrier comprising an organic phase comprising a glyceride derivative and a hydrophilic phase; and (B) a method of treating chronic and neuropathic pain comprising administering to a patient in need thereof the pharmaceutical formulation described in (A).

Discussion of the Examiner's § 103(a) Rejection of Claims 1, 2, and 21 to 38

Claims 1, 2, and 21 to 38 were rejected under § 103(a) as being unpatentable over the teaching of British Patent No. 1,564,039 (hereafter "GB `039") in view of the teachings of Patel et al., *Molecular Pharmacol.*, 46: 943-48 (1994) (hereafter "Patel et al."), and European Application Nos. 0 222 614 and 0 391 369 (hereafter "EP `614" and "EP `369", respectively). (Applicants note that while the

Examiner's Action listed the above-identified British Patent as British Patent No. "1,594,039", it is believed that the Examiner meant British Patent No. 1,564,039.)

The Examiner states that the above claims are rendered obvious because, in the Examiner's view, GB `039 teaches a composition comprising an opioid and a CCK-antagonist, Patel et al. teaches that some CCK-antagonists are poorly water soluble, and EP `614 and EP `369 teach biphasic carriers. According to the Examiner, a person skilled in the art, with knowledge taught by Patel et al. that some CCK-antagonists are poorly water soluble, would have been motivated to combine the composition taught by GB `039 with a biphasic carrier taught by EP `614 or EP `369 to arrive at applicants' invention.

The Examiner's rejection is traversed respectfully. To render a claim obvious, the prior art references must teach or suggest all of the recitations of the claim. MPEP §2143. Claim 1, whose recitations are incorporated in each of the remaining rejected claims, recites a composition which comprises a CCK-antagonist and an opioid. The combined teachings of the cited references do not teach the combination of a CCK-antagonist and an opioid. In his rejection, the Examiner relies upon his view that GB `039 discloses a composition comprising a CCK-antagonist and an opioid. Applicants submit respectfully, however, that the Examiner's view is in error. None of the compounds disclosed by GB `039 is an CCK-antagonist.

Discussion of the Examiner's § 112 Rejection of Claim 24

Claim 24 was rejected by the Examiner under § 112, second paragraph, as being indefinite. Applicants believe that the Examiner's rejection has been rendered moot by the present amendment to Claim 24.

Discussion of the Examiner's Objections to Claims 2 and 21 to 37

The Examiner objected to Claims 2 and 21 to 37 because these dependent claims did not begin with "the". The Examiner objected further to Claim 21 for improper Markush-claim language. Applicants believe that the Examiner's objections have been rendered moot by the present amendments to Claims 2 and 21 to 37.

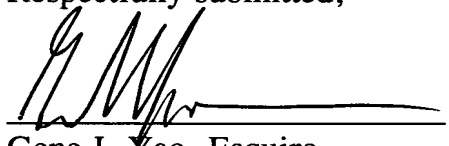
Conclusion

For the reasons expressed above, applicants request respectfully that the Examiner reconsider and withdraw his rejections under 35 U.S.C. §§ 103(a) and 112 as well as his various claim objections.

Attached hereto is a marked-up version of the changes made to the application by the current amendment. The attached version is captioned "Version with Markings to Show Changes Made."

In view of the foregoing amendment and remarks, an early and favorable action is requested respectfully.

Respectfully submitted,



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VERSION WITH MARKINGS TO SHOW CHANGES MADE

2. (Amended) The [A] pharmaceutical formulation according to claim 1, wherein the organic phase (i) has a solubilising capacity for the CCK antagonist in excess of 5mg per gram of organic phase.

21. (Amended) The [A] pharmaceutical formulation according to Claim 1, wherein the organic phase comprises at least one [an] oil selected from the group consisting of soya bean, safflower, sesame, rapeseed, peanut, olive, cotton seed and fish oils and mixtures thereof, alone or in combination with glycerine and/or a wax selected from full and/or partial triglycerides of fatty acids.

22. (Amended) The [A] pharmaceutical formulation according to Claim 1 intended for intravenous use, wherein the hydrophilic phase is aqueous and has a viscosity of from 2500-7500cp at 20°C.

23. (Amended) The [A] pharmaceutical formulation according to Claim 1 intended for use as a solid formulation, wherein the hydrophilic phase is gel

forming, incorporates the opioid in the gel and forms a matrix incorporating the CCK antagonist and the glyceride derivative.

24. (Amended) The [A] pharmaceutical formulation according to Claim 1, wherein the hydrophilic phase comprises a pharmacologically and pharmaceutically acceptable polymer or salt thereof selected from the group consisting of proteins [such as gelatine], hyaluronic acid, alginic acids or salts thereof [such as sodium alginate], carboxymethylcellulose [(optionally cross-linked)], methyl cellulose, other cellulose derivatives which are water-swellable [such as hydroxypropylmethylcellulose and hydroxyethyl-cellulose or], other water-swellable polymers [such as polyvinyl pyrrolidone (PVP) or], and water-soluble polymers [such as lactose].

25. (Amended) The [A] pharmaceutical formulation according to Claim 1, wherein the carrier is in the form of an oil-in-water emulsion.

26. (Amended) The [A] pharmaceutical formulation according to Claim 25, wherein the oil-in-water emulsion comprises

([I]i) an oil phase comprising a glyceride derivative; and

(ii) an aqueous phase optionally comprising a buffer whereby the emulsion has a pH of from 6.5 to 7.5 and optionally comprises an [isotonicty] isotonicity regulator whereby the aqueous phase is made isotonic to blood plasma.

27. (Amended) The [A] pharmaceutical formulation according to Claim 25, wherein the average particle size of the emulsion is from 0.2 to 3.0μm.

28. (Amended) The [A] pharmaceutical formulation according to claim 25 further comprising an emulsifying agent, a surfactant and/or a pH adjuster.

29. (Amended) The [A] pharmaceutical formulation according to Claim 1, wherein the CCK antagonist is incorporated into the organic phase and the opioid is incorporated into the hydrophilic phase.

30. (Amended) The [A] pharmaceutical formulation according to Claim 1, wherein the ratio of component (i) to component (ii) is within the range of 10:1 to 1:5 by weight.

31. (Amended) The [A] pharmaceutical formulation according to Claim 1, wherein the ratio of component (a) to component (b) is within the range of 1:2 to 1:40 by weight.

32. (Amended) The [A] pharmaceutical formulation according to Claim 1, wherein the CCK antagonist is selected from the group consisting of:

3S-(-)-(1,3-dihydro-3-(2-indolecarbonylamino)-1-methyl-5-phenyl-2H-1,4-benzodiazepin-2-one;

3R-3-(N-(3-methylphenyl)ureido)-1,3-dihydro-1-methyl-5-phenyl-2H-1,4-benzodiazepin-2-one;

N-[1,3-dihydro-1-[methy] methyl-2-oxo-5-phenyl-1H-1,4-benzodiazepin-3-yl]-N-[3-(1,2,4-oxodiazol-5-one)phenyl]urea;

(-)-N-[2,3,-dihydro-5-(4,4-dimethylpiperidin-1-yl)-1-methyl-2-oxo-1H-1,4-benzodiazepin-3-yl]-N'-[indan-5-yl]urea; and

[N-[(3R)-5-(3-azabi-cyclo[3.2.2]nonan-3-yl)-2,3-dihydro-1-methyl-2-oxo-1H-1,4-benzodiazepin-3-yl]-N'-(3-methylphenyl)urea].

33. (Amended) The [A] pharmaceutical formulation according to Claim 1, wherein the opioid is selected from the group consisting of morphine,

codeine, or a salt thereof, and 14-hydroxymorphinan opioid analgesics and salts thereof.

34. (Amended) The [A] pharmaceutical formulation according to Claim 1 in the form of a solid formulation, an injectable emulsion, a suppository, or a tablet.

35. (Amended) The [A] pharmaceutical formulation according to Claim 1, in a unit dosage form suitable for the delivery of 0.5 to 300 mg per day of CCK antagonist to a patient in need thereof.

36. (Amended) The [A] pharmaceutical formulation according to Claim 35, in unit dosage form [from] suitable for oral use or use as a suppository for the delivery of 1 to 100mg per day of CCK antagonist to a patient in need thereof.

37. (Amended) The [A] pharmaceutical formulation according to Claim 35 in unit dosage form suitable for intravenous use for the delivery of 1 to 300mg per day of CCK antagonist to a patient in need thereof.